CLAIMS

1. A method for *in vivo* down-regulation of Vascular Endothelial Growth Factor (VEGF) activity in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of

- at least one autologous VEGF protein or an autologous VEGF polypeptide or subsequence thereof which has been formulated so that immunization of the animal with the VEGF protein or VEGF polypeptide or subsequence thereof induces production of antibodies the animal's autologous VEGF protein, and/or

- at least one VEGF analogue, which comprises a VEGF polypeptide wherein is introduced at least one modification in the VEGF amino acid sequence which has as a result that immunization of the animal with the analogue induces production of antibodies against the animal's autologous VEGF protein.

2. The method according to claim 1, wherein is presented a VEGF analogue with at least one modification of the VEGF amino acid sequence.

3. The method according to claim 2, wherein the modification has as a result that a substantial fraction of VEGF B-cell epitopes are preserved and that

- at least one foreign T helper lymphocyte epitope (T_H epitope) is introduced, and/or

- at least one first moiety is introduced which effects targeting of the modified molecule to an antigen presenting cell (APC) or a B-lymphocyte, and/or

- at least one second moiety is introduced which stimulates the immune system, and/or

- at least one third moiety is introduced which optimizes presentation of the modified VEGF polypeptide to the immune system.

4. The method according to claim 3, wherein the modification includes introduction as side groups, by covalent or non-covalent binding to suitable chemical groups in the VEGF polypeptide or a subsequence thereof, of the foreign T_H epitope and/or of the first and/or of the second and/or of the third moiety.

5. The method according to claim 3 or 4, wherein the modification includes amino acid substitution and/or deletion and/or insertion and/or addition.

6. The method according to claim 5, wherein the modification results in the provision of a fusion polypeptide.

7. The method according to claim 5 or 6, wherein introduction of the amino acid substitution and/or deletion and/or insertion and/or addition results in a substantial preservation of the 3D structure of the VEGF polypeptide.

8. The method according to any one of claims 5-7, wherein introduction of the amino acid substitution and/or deletion and/or insertion and/or addition results in a substantial preservation of the overall quarternary structure of the autologous VEGF protein.

9. The method according to any one of claims 2-8, wherein the modification includes duplication of at least one VEGF B-cell epitope and/or introduction of a hapten.

10. The method according to any one of claims 3-9, wherein the foreign T-cell epitope is immunodominant in the animal.

11. The method according to any one of claims 3-10, wherein the foreign T-cell epitope is promiscuous.

12. The method according to claim 11, wherein the at least one foreign T-cell epitope is selected from a natural promiscuous T-cell epitope and an artificial MHC-II binding peptide sequence.

13. The method according to claim 11, wherein the natural T-cell epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope, and wherein the artificial MHC-II binding peptide is a pan DR binding peptide.

14. The method according to any one of claims 3-13, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC specific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC.

15. The method according to any one of claims 3-14, wherein the second moiety is selected from a cytokine, a hormone, and a heat-shock protein.

16. The method according to claim 15, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN-γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and the heat-shock protein is selected from, or is an effective part of any of, HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT).

17. The method according to any one of claims 3-16, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

18. The method according to claim 17, wherein the VEGF polypeptide is a human VEGF-A polypeptide, preferably VEGF-A isoform 121 (SEQ ID NO: 5) or isoform 165 (SEQ ID NO: 4).

19. The method according to claim 18, wherein the human VEGF-A polypeptide has been modified within the N-terminal part proximal to the first beta-strand and/or within the C-terminus of the cystine knot domain and/or within the loop between beta-strands B3 and B4.

20. The method according to claim 19, wherein the human VEGF-A polypeptide has been modified by insertion into, deletionin, addition to, or substitution of any one of amino acids 1-15 in any one of SEQ ID NOs: 2-8.

21. The method according to claim 19 or 20, wherein the human VEGF-A polypeptide has been modified by insertion into, deletion in, addition to, or substitution of any amino acid C-terminal to residue 105 in any one of SEQ ID NOs: 2-8.

22. The method according to any one of claims 19-21, wherein the human VEGF-A polypeptide has been modified by insertion, deletion or substitution in any one of SEQ ID NOs: 2-8, residues 59-66.

23. The method according to any one of the preceding claims, wherein the analogue comprises a structure selected from
$VEGF_m$-X-VEGF, VEGF-X_m-VEGF, VEGF-X-$VEGF_n$, $VEGF_m$-X_m-VEGF, $VEGF_m$-X-$VEGF_n$, VEGF-X_m-$VEGF_n$, and $VEGF_m$-X_m-$VEGF_n$, wherein VEGF is a VEGF polypeptide or subsequence

thereof, X is an inert linker, $VEGF_m$ is a VEGF polypeptide or subsequence thereof that includes a modification constituting or contributing to the presence of the at least one foreign T helper epitope in the analogue, $VEGF_n$ is a VEGF polypeptide or subsequence thereof that includes a modification constituting or contributing to the presence of the at least one foreign T helper epitope in the analogue, and X_m is a peptide linker that includes or contributes to the presence of the at least one foreign T helper epitope in the analogue.

24. The method according to claim 23, wherein the analogue has the formula VEGF-X_m-VEGF.

25. The method according to any one of the preceding claims, wherein presentation to the immune system is effected by having at least two copies of the VEGF polypeptide, the subsequence thereof or the modified VEGF polypeptide covalently of non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

26. The method according to any one of the preceding claims, wherein the VEGF polypeptide, the subsequence thereof, or the modified VEGF polypeptide has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens.

27. The method according to claim 25, wherein the adjuvant is selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (an ISCOM matrix); a particle; DDA; aluminium adjuvants; DNA adjuvants; γ-inulin; and an encapsulating adjuvant.

28. The method according to any one of the preceding claims, wherein an effective amount of the VEGF polypeptide or the VEGF analogue is administered to the animal via a route selected from the parenteral route such as the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; the oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

29. The method according to claim 28, wherein the effective amount is between 0.5 µg and 2,000 µg of the VEGF polypeptide, the subsequence thereof or the analogue thereof.

30. The method according to claim 28 or 29, which includes at least one administration of the VEGF polypeptide or analogue per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year.

31. The method according to any one of claims 28-30, wherein the VEGF polypeptide or analogue is contained in a virtual lymph node (VLN) device.

32. The method according to any one of claims 1-24, wherein presentation of modified VEGF to the immune system is effected by introducing nucleic acid(s) encoding the modified VEGF into the animal's cells and thereby obtaining *in vivo* expression by the cells of the nucleic acid(s) introduced.

33. The method according to claim 32, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with Calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA encapsulated in chitin or chitosan, and DNA formulated with an adjuvant such as the adjuvants defined in claim 26 or 27.

34. The method according to claim 32 or 33, wherein the nucleic acids are administered intraarterially, intraveneously, or by the routes defined in claim 28.

35. The method according to claim 33 or 34, wherein the nucleic acid(s) is/are contained in a VLN device.

36. The method according to any one of claims 33-35, which includes at least one administration of the nucleic acids per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year

37. A method for treating and/or preventing and/or ameliorating diseases selected from the group consisting of malignant neoplasm, benign neoplasm, inflammatory diseases, and diabetes and diabetes related conditions, the method comprising down-regulation of VEGF according to any one of the preceding claims.

38. A VEGF analogue which is derived from an animal VEGF polypeptide wherein is introduced a modification which has as a result that immunization of the animal with the analogue induces production of antibodies against the VEGF polypeptide, and wherein the modification is as defined in any one of claims 1-24.

39. An immunogenic composition comprising an immunogenically effective amount of a VEGF polypeptide autologous in an animal, said VEGF polypeptide being formulated together with an immunologically acceptable adjuvant so as to break the animal's autotolerance towards the VEGF polypeptide, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle.

40. An immunogenic composition comprising an immunogenically effective amount of a VEGF analogue according to claim 38, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.

41. An immunogenic composition according to Claim 39 or 40, wherein the adjuvant is selected from the group consisting of the adjuvants of claim 26 or 27.

42. A nucleic acid fragment which encodes a VEGF analogue according to claim 38.

43. A vector carrying the nucleic acid fragment according to claim 42.

44. The vector according to claim 43 which is capable of autonomous replication.

45. The vector according to claim 43 or 44 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

46. The vector according to any one of claims 43-45, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 42, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 42, and optionally a terminator.

47. The vector according to any one of claims 43-46 which, when introduced into a host cell, is integrated in the host cell genome.

48. The vector according to any one of claims 43-46 which, when introduced into a host cell, is not capable of being integrated in the host cell genome.

49. The vector according to any one of claims 43-48, wherein the promoter drives expression in a eukaryotic cell and/or in a prokaryotic cell.

50. A transformed cell carrying the vector of any one of claims 43-49.

51. The transformed cell according to claim 50 which is capable of replicating the nucleic acid fragment according to claim 42.

52. The transformed cell according to claim 51, which is a microorganism selected from a bacterium, a yeast, a protozoan, or a cell derived from a multicellular organism selected from a fungus, an insect cell such as an S_2 or an SF cell, a plant cell, and a mammalian cell.

53. The transformed cell according to claim 52 which is a bacterium of the genus *Escherichia*, *Bacillus*, *Salmonella*, or *Mycobacterium*.

54. The transformed cell according to claim 53, which is selected from the group consisting of an *E. coli* cell, and a non-pathogenic *Mycobacterium* cell such as *M. bovis* BCG.

55. The transformed cell according to any one of claims 50-54, which expresses the nucleic acid fragment according to claim 42.

56. The transformed cell according to claim 55, which secretes or carries on its surface, the VEGF analogue according to claim 38.

57. The method according to any one of claims 1-24, wherein presentation to the immune system is effected by administering a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment which encodes and expresses the VEGF polypeptide or analogue.

58. The method according to claim 57, wherein the virus is a non-virulent pox virus such as a vaccinia virus.

59. The method according to claim 58, wherein the microorganism is a bacterium, such as a bacterium defined in claim 53 or 54.

60. The method according to any one of claims 57-59, wherein the non-pathogenic microorganism or virus is administered one single time to the animal.

61. A composition for inducing production of antibodies against VEGF, the composition comprising

- a nucleic acid fragment according to claim 42 or a vector according to any one of claims 43-49, and

- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

62. The composition according to claim 61, wherein the nucleic acid fragment is formulated according to claim 33 or 35.

63. A stable cell line which carries the vector according to any one of claims 43-49 and which expresses the nucleic acid fragment according to claim 42, and which optionally secretes or carries the VEGF analogue according to claim 38 on its surface.

64. A method for the preparation of the cell according to any one of claims 50-56, the method comprising transforming a host cell with the nucleic acid fragment according to claim 42 or with the vector according to any one of claims 43-49.